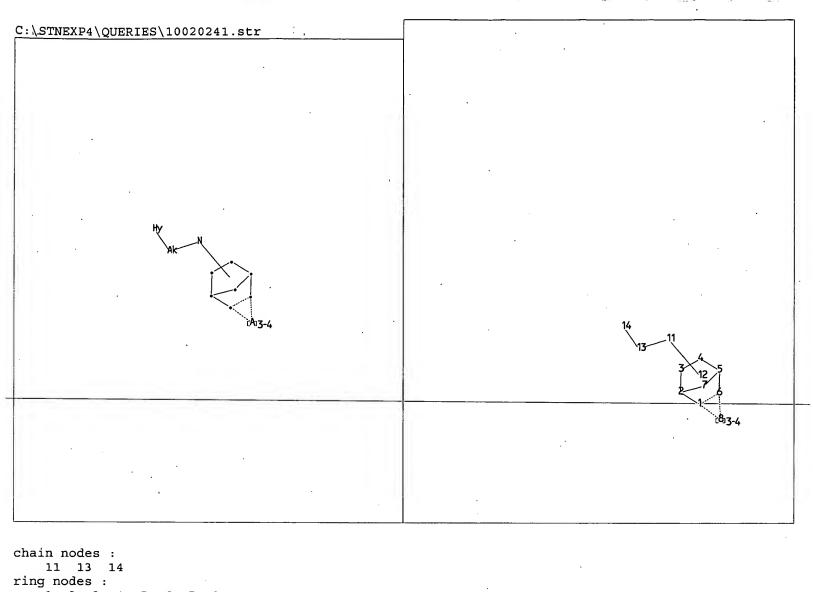
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|          | ·    | (546/285) or (548/202) or (548/335.5) or     | US-PGPUB;            | <u> </u>         |
|          |      | (548/528) or (549/74) or (549/492)).CCLS.    | EPO; JPO;<br>DERWENT |                  |
| 2        | 6577 | ((514/247) or (514/252.1) or (514/256) or    | USPAT;               | 2003/07/09 19:34 |
|          |      | (514/365) or (514/427) or (514/400) or       | US-PGPUB;            |                  |
|          |      | (514/438) or (514/471) or (514/357)).CCLS.   | EPO; JPO;<br>DERWENT |                  |
| 3        | 9390 | (((544/224) or (544/294) or (544/336) or     | USPAT;               | 2003/07/09 19:35 |
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|          |      | (548/528) or (549/74) or (549/492)).CCLS.)   | EPO; JPO;            |                  |
|          |      | or (((514/247) or (514/252.1) or (514/256)   | DERWENT              |                  |
|          |      | or (514/365) or (514/427) or (514/400) or    |                      |                  |
|          |      | (514/438) or (514/471) or (514/357)).CCLS.)  |                      |                  |
| 4        | 8029 | octahydro\$ .                                | USPAT;               | 2003/07/09 19:37 |
|          |      |  | US-PGPUB;            |                  |
|          |      |  | EPO; JPO;            | ·                |
|          |      |  | DERWENT              |                  |
| 5        | 282  | 1      | USPAT;               | 2003/07/09 19:37 |
| }        |      | (546/285) or (548/202) or (548/335.5) or     | US-PGPUB;            |                  |
|          |      | (548/528) or (549/74) or (549/492)).CCLS.)   | EPO; JPO;            |                  |
|          |      | or (((514/247) or (514/252.1) or (514/256)   | DERWENT              |                  |
|          |      | or (514/365) or (514/427) or (514/400) or    |                      |                  |
|          |      | (514/438) or (514/471) or (514/357)).CCLS.)) |                      | ]                |
|          |      | _and_octahydro\$                             |                      | L                |

Page 1



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1 2 3 4 5 6 7 8
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   11-13 13-14
ring bonds :
   1-2 1-6 1-8 2-3 2-7 3-4 4-5 5-6 5-7 6-8
exact/norm bonds :
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exact bonds :
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isolated ring systems :
   containing 1 :
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   Number of Carbon Atoms : less than 7
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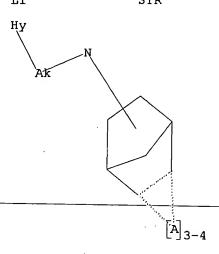
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Structure attributes must be viewed using STN Express query preparation.

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30.8% PROCESSED 1000 ITERATIONS INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)

SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS: ONLINE \*\*COMPLETE\*\*

BATCH \*\*COMPLETE\*\*

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PROJECTED ANSWERS:

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100.0% PROCESSED 65351 ITERATIONS

72 ANSWERS

1 ANSWERS

SEARCH TIME: 00.00.01

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16 L3

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     Preparation of methanoindenylaminomethylheterocycles and related compounds
TI
     as inhibitors of the sodium-proton exchanger.
IN
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PA
     Aventis Pharma Deutschland G.m.b.H., Germany
     Ger. Offen., 20 pp.
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os
    Title compds. [I; A = alkylene; T = H, alkyl; B = (substituted) (unsatd.)
AB
     exo- or endo 5-6 membered ring; X = (unsatd.) 5-6 membered heterocyclyl; n
     = 0-4; with a proviso], were prepd. Thus, endo/exo-octahydro-4,7-
     methanoinden-5-ylamine (prepn. given), pyridine-3-carboxaldehyde, and
     p-toluenesulfonic acid were refluxed in PhMe through a water separator.
     The residue in MeOH was treated with NaBH4 followed by acidification with
     HCl to give endo/exo-(octahydro-4,7-methanoinden-5-yl)pyridin-3-
     ylmethylamine hydrochloride. The latter showed rat Na+/H+ exchanger 3
     (NHE3) inhibitory activity with IC50 = 0.34 .mu.M.
IT
     440114-58-9P 440114-63-6P 440114-68-1P
     440114-73-8P 440114-77-2P 440114-79-4P
     440114-81-8P 440114-85-2P 440114-90-9P
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     440116-60-9P
     RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
     (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
     (Uses)
```

inhibitors of the sodium-proton exchanger)

(prepn. of methanoindenylaminomethylheterocycles and related compds. as

RN 440114-58-9 CAPLUS

CN 3-Pyridinemethanamine, N-[(3aR, 4S, 5R, 7S, 7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, dihydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

## •2 HCl

RN 440114-63-6 CAPLUS

CN 2-Furanmethanamine, N-[(3aR,4S,5R,7S,7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

#### HCl

RN 440114-68-1 CAPLUS

CN 2-Thiophenemethanamine, N-[(3aR, 4S, 5R, 7S, 7aR)-octahydro-4, 7-methano-1H-inden-5-yl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

## • HCl

RN 440114-73-8 CAPLUS

CN 3-Pyridinemethanamine, N-[(3aR, 4R, 5S, 7R, 7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, dihydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

## ●2 HCl

RN 440114-77-2 CAPLUS

CN 2-Pyridinemethanamine, 3-chloro-N-[(3aR,4S,5R,7S,7aR)-octahydro-4,7-methano-1H-inden-5-yl]-5-(trifluoromethyl)-, rel-, trifluoroacetate (9CI) (CA INDEX NAME)

CM 1

CRN 440114-76-1 CMF C17 H20 C1 F3 N2

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 440114-79-4 CAPLUS

CN 3-Pyridinemethanamine, N-[(1R,2S,4R,4aS,8aS)-decahydro-1,4-methanonaphthalen-2-yl]-, dihydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

#### ●2 HCl

RN 440114-81-8 CAPLUS

CN 3-Furanmethanamine, N-[(3aR,4S,5R,7S,7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

RN 440114-85-2 CAPLUS

CN 2-Furanmethanamine, 5-ethyl-N-[(3aR, 4S, 5R, 7S, 7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

## HCl

RN 440114-90-9 CAPLUS

CN 3-Thiophenemethanamine, N-[(3aR,4S,5R,7S,7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

HCl

RN 440114-95-4 CAPLUS

CN 2-Pyridinemethanamine, N-[(3aR, 4S, 5R, 7S, 7aR)-octahydro-4, 7-methano-1H-inden-5-yl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

#### ●x HCl

RN 440114-99-8 CAPLUS

CN 4-Pyridinemethanamine, N-[(3aR,4S,5R,7S,7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

#### •x HCl

RN 440115-02-6 CAPLUS

CN 1H-Imidazole-4-methanamine, N-[(3aR, 4S, 5R, 7S, 7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

RN 440115-06-0 CAPLUS

CN 1H-Imidazole-2-methanamine, N-[(3aR,4S,5R,7S,7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

#### •x HCl

RN 440115-10-6 CAPLUS

CN 1H-Pyrrole-2-methanamine, N-[(3aR, 4S, 5R, 7S, 7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, monohydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

HCl

RN 440115-13-9 CAPLUS

CN 2-Thiazolemethanamine, N-[(3aR, 4S, 5R, 7S, 7aR)-octahydro-4, 7-methano-1H-inden-5-yl]-, monohydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

● HCl

-RN---440-1-15=1-7=3\_\_CAPLUS

CN Pyrazinemethanamine, N-[(3aR, 4S, 5R, 7S, 7aR)-octahydro-4,7-methano=1H-inden-5-yl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

•x HCl

RN 440115-20-8 CAPLUS

CN 5-Pyrimidinemethanamine, N-[(3aR,4S,5R,7S,7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

RN 440115-25-3 CAPLUS

CN 4-Pyridazinemethanamine, N-[(3aR, 4S, 5R, 7S, 7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

## Relative stereochemistry.

# •x HCl

RN 440115-30-0 CAPLUS

CN 1H-Pyrazole-3-methanamine, N-[(3aR,4S,5R,7S,7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

RN 440115-34-4 CAPLUS

CN 3-Pyridinemethanamine, N-[(3aR, 4R, 6S, 7R, 7aS)-3a, 4, 5, 6, 7, 7a-hexahydro-4, 7-methano-1H-inden-6-yl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

## ●x HCl

RN 440115-38-8 CAPLUS

CN 3-Pyridinemethanamine, N-[(3aR,4S,5R,7S,7aR)-3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl]-, hydrochloride, rel- (9CI) (CA INDEX NAME)

RN 440115-41-3 CAPLUS

-CM----:

CRN 440115-40-2 CMF C16 H21 C12 N S

Relative stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 440115-44-6 CAPLUS

CN 1H-Pyrazole-1-propanamine, .alpha.-methyl-N-[(3aR,4S,5R,7S,7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, rel-, trifluoroacetate (9CI) (CA INDEX NAME)

CM 1

CRN 440115-43-5 CMF C17 H27 N3

Relative stereochemistry.

$$\begin{array}{c|c} & & & & \\ & & & \\ N & & & \\ N & & \\ N & & \\ Me & & \\ & &$$

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 440115-49-1 CAPLUS

CN 3-Thiophenemethanamine, 5-nitro-N-[(3aR,4S,5R,7S,7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, rel-, mono(trifluoroacetate) (9CI) (CA INDEX NAME)

CM 1

CRN 440115-48-0 CMF C15 H20 N2 O2 S

Relative stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 440115-54-8 CAPLUS

CN 1H-Pyrazole-4-methanamine, 5-chloro-3-methyl-N-[(3aR,4S,5R,7S,7aR)-octahydro-4,7-methano-1H-inden-5-yl]-1-phenyl-, rel-, trifluoroacetate (9CI) (CA INDEX NAME)

CM 1

CRN 440115-53-7 CMF C21 H26 C1 N3

#### Relative stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 440115-57-1 CAPLUS

ON 3-Isoxazolecarboxylic acid, 5-[1-[[(3aR,4S,5R,7S,7aR)-octahydro-4,7-methano-1H-inden-5-yl]amino]ethyl]-, ethyl ester, rel-, trifluoroacetate (9CI) (CA INDEX NAME)

CM 1

CRN 440115-56-0

CMF C18 H26 N2 O3

Relative stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 440115-76-4 CAPLUS

CN 3-Pyridinemethanamine, N-[(3aR, 4R, 5S, 7R, 7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 440115-81-1 CAPLUS

CN 3-Pyridinemethanamine, N-[(3aR, 4S, 5R, 7S, 7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, rel- (9CI) (CA INDEX NAME)

RN 440115-85-5 CAPLUS

CN Pyrazinemethanamine, N-[(3aR,4S,5R,7S,7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 440115-89-9 CAPLUS

CN 2-Thiophenemethanamine, N-[(3aR, 4S, 5R, 7S, 7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 440115-93-5 CAPLUS

CN 3-Thiophenemethanamine, N-[(3aR, 4S, 5R, 7S, 7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, rel- (9CI) (CA INDEX NAME)

RN 440115-97-9 CAPLUS

CN 3-Pyridinemethanamine, N-[(3aR, 4R, 6S, 7R, 7aS)-3a, 4, 5, 6, 7, 7a-hexahydro-4, 7-methano-1H-inden-6-yl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 440116-01-8 CAPLUS

CN 3-Pyridinemethanamine, N-[(3aR, 4S, 5R, 7S, 7aR)-3a, 4, 5, 6, 7, 7a-hexahydro-4, 7-methano-1H-inden-5-yl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 440116-07-4 CAPLUS

CN 3-Furanmethanamine, N-[(3aR, 4S, 5R, 7S, 7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, rel- (9CI) (CA INDEX NAME)

RN 440116-13-2 CAPLUS

CN 2-Furanmethanamine, N-[(3aR,4S,5R,7S,7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 440116-17-6 CAPLUS

CN 3-Pyridinemethanamine, N-[(1R,2S,4R,4aS,8aS)-decahydro-1,4-methanonaphthalen-2-yl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 440116-23-4 CAPLUS

CN 1H-Pyrrole-2-methanamine, N-[(3aR, 4S, 5R, 7S, 7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, rel- (9CI) (CA INDEX NAME)

RN 440116-27-8 CAPLUS

CN 5-Pyrimidinemethanamine, N-[(3aR,4S,5R,7S,7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 440116-32-5 CAPLUS

CN 3-Pyridinemethanamine, N-[(3aR,4R,5S,7R,7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, rel-, trifluoroacetate (9CI) (CA INDEX NAME)

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CRN 440115-76-4 CMF C16 H22 N2

Relative stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

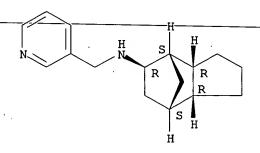
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CN 3-Pyridinemethanamine, N-[(3aR, 4S, 5R, 7S, 7aR) -octahydro-4, 7-methano-1H-inden-5-yl]-, rel-, trifluoroacetate (9CI) (CA INDEX NAME)

CM 1

CRN 440115-81-1 CMF C16 H22 N2

Relative stereochemistry.



CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 440116-42-7 CAPLUS

CN Pyrazinemethanamine, N-[(3aR,4S,5R,7S,7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, rel-, trifluoroacetate (9CI) (CA INDEX NAME)

CM 1

CRN 440115-85-5 CMF C15 H21 N3

CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 440116-45-0 CAPLUS

CN 2-Thiophenemethanamine, N-[(3aR, 4S, 5R, 7S, 7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, rel-, trifluoroacetate (9CI) (CA INDEX NAME)

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Relative stereochemistry.

CM 2

CRN 76-05-1 CMF C2 H F3 O2

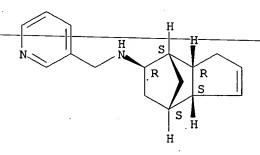
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CM 1

CRN 440115-97-9 CMF C16 H20 N2

Relative stereochemistry.



CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 440116-53-0 CAPLUS

CN 3-Pyridinemethanamine, N-[(3aR,4S,5R,7S,7aR)-3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl]-, rel-, trifluoroacetate (9CI) (CA-INDEX NAME)

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CM 2

CRN 76-05-1 CMF C2 H F3 O2

RN 440116-57-4 CAPLUS

CN 3-Pyridinemethanamine, N-[(1R,2S,4R,4aS,8aS)-decahydro-1,4-methanonaphthalen-2-yl]-, rel-, trifluoroacetate (9CI) (CA INDEX NAME)

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Relative stereochemistry.

CM 2

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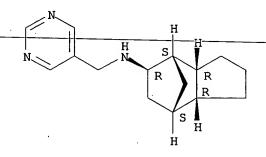
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CN 5-Pyrimidinemethanamine, N-[(3aR,4S,5R,7S,7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, rel-, trifluoroacetate (9CI) (CA INDEX NAME)

CM 1

CRN 440116-27-8 CMF C15 H21 N3

Relative stereochemistry.



CM 2

CRN 76-05-1 CMF C2 H F3 O2

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4

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ANSWER 2 OF 16 CAPLUS COPYRIGHT 2003 ACS
AN
     2001:152650 CAPLUS
DN
     134:207831
TI
     Preparation, composition and use of heterocyclic aromatic amides as
     fungicides
     Ricks, Michael John; Dent, William Hunter, III; Rogers, Richard Brewer;
IN
     Yao, Chenglin; Nader, Bassam Salim; Miesel, John Louis; Fitzpatrick, Gina
     Marie; Meyer, Kevin Gerald; Niyaz, Noormohamed Mohamed; Morrison, Irene
     Mae; Henry, Matthew James; Adamski, Butz Jenifer Lynn; Gajewski, Robert
PA
     Dow Agrosciences LLC, USA
SO
     PCT Int. Appl., 200 pp.
     CODEN: PIXXD2
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     Patent
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|      | US 20 | 000-620662    | Ά  | 20000720 |    |            |          |
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|      | EP 20 | 000-952599    | A3 | 20000804 |    |            |          |
|      | US 20 | 000-632930    | A3 | 20000804 |    |            |          |
|      | WO 20 | 000-US21523   | W  | 20000804 |    | _          | •        |
| os   | MARPA | AT 134:207831 |    |          |    |            |          |

AB Title compds. [I; wherein X1-X4 independently = O, S, NR1, N, CR2, bond; R1 = H, C1-3 alkyl, C2-3 alkenyl, C2-3 alkynyl, OH, CHF2, C1-4 alkoxy; R2 = H, F, C1, Br, CN, OH, C1-3 alkyl, C1-3 haloalkyl cyclopropyl, C1-3 alkoxy; Z = O, S, NOH, NOR3; R3 = C1-3 alkyl; A = C1-14 alkyl, C1-14 alkynyl, C1-14 cycloalkyl, aryl, heteroaryl, Q; M = H, Si(t-Bu)Me2, Si(Ph)Me2, SiEt3, CZR4, SO2R5; R4 = H, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl; R5 = 1aryl, heteroaryl, C1-6 alkyl, C2-6 alkenyl, C3-6 alkenyl, C3-6 alkynyl, C3-6 cycloalkyl; X, Y independently = O, S; W = O, CH2, bond; R = C1-8alkyl, C2-8 alkenyl, C2-8 alkynyl, C3-8 cycloalkyl, aryl, heteroaryl; R11 = H, C1-3 alkyl, C2-5 alkenyl, C2-5 alkynyl; R10 = H, R, OR, OCOR, OCOOR; R8, R9 independently = H, C1-6 alkyl, C2-6 alkenyl; R6, R7 independently = H, C1-6 alkyl, C2-6 alkenyl, C2-5 alkynyl, C3-6 cycloalkyl] are prepd. as fungicides involving application methods of effective usage of title compds. to control fungi, particularly plant pathogens and wood-decayingfungi. The invention also encompasses hydrates, salts and complexes thereof. The title compd. II was prepd. and tested as fungicide.

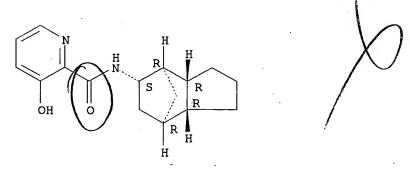
IT 321597-85-7P 321597-86-8P 321598-57-6P 321598-69-0P 321598-70-3P

RL: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses) (prepn. and fungicidal activity of heterocyclic arom. amides)

RN 321597-85-7 CAPLUS

CN 2-Pyridinecarboxamide, 3-hydroxy-N-[(3aR,4R,5S,7R,7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 321597-86-8 CAPLUS

CN 2-Pyridinecarboxamide, 3-hydroxy-N-[(3aR,4R,5R,6R,7S,7aS)-octahydro-6-hydroxy-4,7-methano-1H-inden-5-yl]-, rel- (9CI) (CA INDEX NAME)

RN 321598-57-6 CAPLUS

CN 2-Pyridinecarboxamide, 3-hydroxy-4-methoxy-N-[(1R,2S,4R)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-yl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 321598-69-0 CAPLUS

CN 2-Pyridinecarboxamide, 3-hydroxy-4-methoxy-N-[(3aR,4S,5R,7S,7aS)-octahydro-4,7-methanoisobenzofuran-5-yl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 321598-70-3 CAPLUS

CN 2-Pyridinecarboxamide, 3-hydroxy-4-methoxy-N-[(3aR, 4S, 5R, 7S, 7aS)-octahydro-2-(2-methylpropyl)-1,3-dioxo-4,7-methano-1H-isoindol-5-yl]-, rel- (9CI) (CA INDEX NAME)

MeO OH O 
$$\frac{H}{N}$$
  $\frac{H}{N}$   $\frac{H}{N}$   $\frac{H}{N}$   $\frac{H}{N}$   $\frac{H}{N}$   $\frac{Bu-i}{N}$ 

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ANSWER 3 OF 16 CAPLUS COPYRIGHT 2003 ACS
L4
AN
     2001:63978
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DN
     134:131431
ΤI
     Fungicidal heterocyclic aromatic amides and their compositions, methods of
     use and preparation
     Ricks, Michael John; Dent, William Hunter, III; Rogers, Richard Brewer;
IN
     Yao, Chenglin; Nader, Bassam Salim; Miesel, John Louis; Fitzpatrick, Gina
     Marie; Meyer, Kevin Gerald; Niyaz, Noormohamed Mohamed; Morrison, Irene
     Mae; Gajewski, Robert Peter
PA
     Dow Agrosciences LLC, USA
SO
     PCT Int. Appl., 159 pp.
     CODEN: PIXXD2
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     Patent
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             SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW,
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PRAI US 1999-144676P
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     US 1999-149977P
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     WO 2000-US19794
                       W
                            20000720
     US 2000-632930
                       А3
                            20000804
OS
     MARPAT 134:131431
AB
     Title compds. I [W, X, Y, Z are selected from S, O, NR1, N, CR2 or bond
     and comprise a 5-6 membered (un) substituted heterocyclic ring; R1 = H,
     alkyl, alkenyl, alkynyl, OH, acyloxy, alkoxymethyl, CHF2, cyclopropyl, or
     alkoxy; R2 = H, halo, CN, OH, alkyl, haloalkyl, cyclopropyl, alkoxy,
     haloalkoxy, etc.; G = O, S or NOR3 where R3 = H or alkyl; A =
     (un) substituted alkyl, alkenyl, alkynyl, cycloalkyl, unsatd. cycloalkyl,
     heterocycle, bi or tricyclic ring system which may contain heteroatoms,
     aryl or heteroaryl, etc.] bearing a hydroxy group adjacent to the amide
     functionality are prepd. and disclosed as antifungal agents, particularly
     for plants. Thus, pyridinyl carboxamide II was prepd. via amidation of
     3-benzyloxy-6-bromo-4-methoxypyridin-2-carbonyl chloride with
     4-(4-trifluoromethylphenoxy) aniline with subsequent deprotection.
     preferred fungicidal compn. consists of a compd. of formula I with a
     phytol. acceptable carrier. Activity has been demonstrated against a
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variety of fungi, e.g., Plasmopara viticola (Downy Mildew of Grape),

Phytophthora infestans (Late Blight of Tomato), and Venturia inaequalis (Apple Scab). I is both useful for eradication and prevention of fungal attack.

IT 321597-85-7P 321597-86-8P 321598-57-6P 321598-69-0P 321598-70-3P

RL: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses) (prepn. and fungicidal activity of heterocyclic arom. amides)

RN 321597-85-7 CAPLUS

CN 2-Pyridinecarboxamide, 3-hydroxy-N-[(3aR,4R,5S,7R,7aR)-octahydro-4,7-methano-1H-inden-5-yl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 321597-86-8 CAPLUS

CN 2-Pyridinecarboxamide, 3-hydroxy-N-[(3aR,4R,5R,6R,7S,7aS)-octahydro-6-hydroxy-4,7-methano-1H-inden-5-yl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 321598-57-6 CAPLUS

CN 2-Pyridinecarboxamide, 3-hydroxy-4-methoxy-N-[(1R,2S,4R)-1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-yl]-, rel- (9CI) (CA INDEX NAME)

RN 321598-69-0 CAPLUS

CN 2-Pyridinecarboxamide, 3-hydroxy-4-methoxy-N-[(3aR,4S,5R,7S,7aS)-octahydro-4,7-methanoisobenzofuran-5-yl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 321598-70-3 CAPLUS

CN 2-Pyridinecarboxamide, 3-hydroxy-4-methoxy-N-[(3aR,4S,5R,7S,7aS)-octahydro-2-(2-methylpropyl)-1,3-dioxo-4,7-methano-1H-isoindol-5-yl]-, rel- (9CI) (CA INDEX NAME)

MeO OH O 
$$\frac{H}{N}$$
  $\frac{H}{S}$   $\frac{H}{R}$   $\frac{O}{S}$   $\frac{Bu-i}{H}$ 

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L4
     ANSWER 4 OF 16 CAPLUS COPYRIGHT 2003 ACS
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     2001:10086 CAPLUS
     134:86277
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ΤI
     1,3-Diazines with platelet-derived growth factor receptor inhibitory
IN
     Matsuno, Kenji; Ichimura, Michio; Nomoto, Yuji; Fujiwara, Shigeki; Ide,
     Shinichi; Tsukuda, Eiji; Irie, Junko; Oda, Shoji
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     Kyowa Hakko Kogyo Co., Ltd., Japan
SO
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     CODEN: USXXAM
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OS
    MARPAT 134:86277
AB
     1,3-Diazines and related N heterocycles [I; wherein V = O or S; W = O
     1,4-piperazinediyl or 1,4-homopiperazinediyl which may be substituted with
     unsubstituted alkyl on the ring; X = N or CR9; Y = N or CR8; Z = N or CR7,
     with at least one of X, Y and Z being N; R1 = H, (un)substituted alkyl,
     cycloalkyl, aryl, heterocyclyl, etc.; R2 = substituted alkyl,
     (un) substituted cycloalkyl, aryl, heterocyclyl, etc.; R3, R4, R5, R6 = H,
     halo, (un)substituted alkyl, NO2, cyano, (un)substituted OH or NH2, etc.;
     R7, R8 = R1 groups, halo, etc.; R9 = H, CO2H or derivs.] and their pharmacol. acceptable salts are prepd. These compds. inhibit the
     phosphorylation of PDGF receptors and the abnormal proliferation or
     migration of cells, and so are effective in preventing or treating cell
     proliferative diseases such as arteriosclerosis, vascular reocclusion
     diseases, cancer, and glomerulosclerosis. Thus, 6,7-dimethoxy-4-(1-
     piperazinyl)quinazoline reacted with Ph isocyanate in refluxing EtOH to
     give invention compd. II [R = CONHPh] in 44% isolated yield. The analog
     II [R = Q] showed an IC50 of 0.03 .mu.M for inhibiting the phosphorylation
     of PDGF receptor in vitro. Pharmaceutical formulations, e.g. tablets
     contg. II [R = N-(p-nitrophenyl) carbamoyl], were prepd.
     205264-16-0P
    RL: BAC (Biological activity or effector, except adverse); BSU (Biological
     study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use);
     BIOL (Biological study); PREP (Preparation); USES (Uses)
        (prepn. of 1,3-diazines with platelet-derived growth factor receptor
        inhibitory activity)
RN
     205264-16-0 CAPLUS
CN
     1-Piperazinecarbothioamide, 4-(6,7-dimethoxy-4-quinazolinyl)-N-
     [(3aR, 4S, 5R, 7S, 7aR)-3a, 4, 5, 6, 7, 7a-hexahydro-4, 7-methano-1H-inden-5-y1]-,
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Relative stereochemistry.

rel- (9CI)

(CA INDEX NAME)

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

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ANSWER 5 OF 16 CAPLUS COPYRIGHT 2003 ACS
L4
AN
     2000:53602
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     132:108299
ΤI
     Preparation of precursors for PNA monomers
IN
    Martens, Jurgen; Maison, Wolfgang; Schlemminger, Imre; Westerhoff, Ole;
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     Germany
     PCT Int. Appl., 72 pp.
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PRAI WO 1998-EP4281
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    MARPAT 132:108299
     Compds: X=CO=E=N-(D-Y)-CO-A-B-[A-is-a-single-bond,-o-phenylene,-or-a-group-
AB
     (CR1R2)n (n = 1-3, R1, R2 = H, OH, amino, F, Cl, Br, iodo, aryl, or alkyl
     optionally substituted by amino, hydroxy, alkoxy, or alkylthio); B = H,
     alkyl, nucleobases, arom. or heterocyclic moieties, DNA intercalators,
     nucleobase-binding groups, reporter ligands, vinyl, Cl, Br, iodo, OH; D =
     o-phenylene or CR3R4CR5R6 (R3, R4, R5, R6 = H, alkyl, or aryl optionally
     substituted by alkyl, OH, alkoxy, nitro, aryl, alkoxycarbonyl, halo, or
     carbohydrate moieties or R3 and R5 or R3 and R4 taken together complete an
    alicyclic system); E is CR7R8 (R7, R8 = H, alkyl, or aryl optionally
     substituted by alkyl, OH, alkoxy, nitro, aryl, alkoxycarbonyl, halo, or
     carbohydrate moieties or R7 and R8 taken together complete an alicyclic or
     heterocyclic system which may be substituted by alkyl, OH, alkoxy, nitro,
     aryl, alkoxycarbonyl, or halo groups); X is R10R11:CR9NH (R9, R10, R11 =
    H, alkyl, or aryl or R9 and R10 taken together with the vinyl group
     complete a five- or six-membered alicyclic system or a heteroarom. system,
     each of which may be substituted); Y is NR12R13 (R12, R13 = H, an amino
    protecting group, OR14 or SR14, where R14 is H or a protecting group)]
    were prepd. as precursors for PNA monomers. Thus, 1-cyclohexenyl
    isocyanide was added to a stirred mixt. of mono-Boc-ethylenediamine (Boc =
    tert-butoxycarbonyl), 4-nitrobenzaldehyde, and N4-Z-N-1-
     carboxymethylcytosine (Z = benzyloxycarbonyl) in methanol and the mixt.
    heated for five minutes to reflux and stirred for 48 h at room temp. to
     afford 36% rac-2-[(2'-Boc-aminoethyl)-N4-Z-cytosineacetyl-amino]-p-
    nitrophenylacetic acid cyclohexen-1''-ylamide.
     255736-48-2P
IT
    RL: SPN (Synthetic preparation); PREP (Preparation).
        (prepn. of precursors for PNA monomers)
ŔŃ
    255736-48-2 CAPLUS
    Carbamic acid, [2-[[(3,4-dihydro-5-methyl-2,4-dioxo-1(2H)-
    pyrimidinyl)acetyl][octahydro-5-[[(4-methoxy-2-nitrophenyl)amino]carbonyl]-
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4,7-methano-1H-inden-5-yl]amino]ethyl]-, 1,1-dimethylethyl ester (9CI)

(CA INDEX NAME)

$$\begin{array}{c|c} & & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ & &$$

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

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L4
     ANSWER 6 OF 16 CAPLUS COPYRIGHT 2003 ACS
ΑN
     1998:219795 CAPLUS
DN
     128:257447
ΤI
     Preparation of nitrogenous heterocyclic compounds inhibiting
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IN
     Matsuno, Kenji; Ichimura, Michio; Nomoto, Yuji; Fujiwara, Shigeki; Ide,
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                                           WO 1997-JP3510
                                                             19971001
         W: AU, BG, BR, CA, CN, CZ, HU, JP, KR, MX, NO, NZ, PL, RO, SG, SI,
             SK, UA, US, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
     CA 2239227
                       AΑ
                            19980409
                                            CA 1997-2239227 19971001
     AU 9744708
                       A1-
                            19980424-
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     AU 719392
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     EP 882717 ·
                            19981209
                       A1
                                            EP 1997-943133
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             AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, FI
     CN 1208404
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                                            CN 1997-191741
                       Α
                                                             19971001
     MX 9804356
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                       Α
                            20000831
                                                             19980601
     US 6169088
                            20010102
                                           US 1998-88199
                       B1
                                                             19980601
     US 6207667
                       B1
                            20010327
                                           US 2000-481544
                                                             20000112
     US 2002068734
                       A1
                            20020606
                                           US 2000-734918
                                                             20001213
     US 6472391
                       B2
                            20021029
PRAI JP 1996-260743
                       Α.
                            19961001
     WO 1997-JP3510
                       W
                            19971001
     US 1998-88199
                       Α3
                            19980601
     US 2000-481544
                       A3
                            20000112
OS
     MARPAT 128:257447
     Nitrogenous heterocyclic compds. of general formula [I; wherein V is
AΒ
     oxygen or sulfur; W is 1,4-piperazinediyl or 1,4-homopiperazinediyl which
     may be substituted with unsubstituted alkyl on the ring; X is nitrogen or
     C-R9; Y is nitrogen or C-R8; Z is nitrogen or C-R7, with at least one of
     X, Y and Z being nitrogen; Rl is hydrogen, substituted or unsubstituted
     alkyl, substituted or unsubstituted cycloalkyl or the like; R2 is
     substituted alkyl, substituted or unsubstituted cycloalkyl or the like;
     R3, R4, R5 and R6 are each independently hydrogen, halogeno, substituted
     or unsubstituted alkyl, nitro, cyano, (un) substituted OH or NH2 or the
     like; R7, R8 = R1, halogeno or the like; R9 is hydrogen or acyl] and
     pharmacol. acceptable salts thereof are prepd. These compds. inhibit the
     phosphorylation of PDGF acceptors and the abnormal proliferation or
     migration of cells and so are effective in preventing or treating cell
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proliferative diseases such as arterial sclerosis, vascular reocclusion

diseases, cancer, and glomerulosclerosis. Thus, 6.7-dimethoxy-4-piperazinylquinazoline was dissolved in ethanol, followed by adding Ph isocyanate, and the resulting mixt. was heated at reflux for 10 min to give 4(4-quinazolinyl)piperazine deriv. (II; R = CONHPh). II (R = Q) in vitro showed IC50 of 0.03 .mu.M for inhibiting the phosphorylation of PDGF

receptor. Pharmaceutical formulations, e.g. tablet contg. II (R =

N-p-nitrophenylcarbamoyl), were prepd.

#### IT 205264-16-0P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(prepn. of nitrogenous heterocyclic compds. inhibiting phosphorylation of platelet-derived growth factors (PDGF) receptors)

RN 205264-16-0 CAPLUS

CN 1-Piperazinecarbothioamide, 4-(6,7-dimethoxy-4-quinazoliny1)-N[(3aR,4S,5R,7S,7aR)-3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-5-yl]-,
rel- (9CI) (CA INDEX NAME)

RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD ALL CITATIONS AVAILABLE IN THE RE FORMAT

- L4 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2003 ACS
- AN 1997:311258 CAPLUS
- DN 127:5085
- TI Pyrazole derivatives as cannabinoid receptor agonists
- IN Barth, Francis; Casellas, Pierre; Congy, Christian; Martinez, Serge; Rinaldi, Murielle; Anne-Archard, Gilles
- PA Sanofi, Fr.
- SO U.S., 45 pp., Cont.-in-part of U.S. Ser. No. 168,237, abandoned. CODEN: USXXAM
- DT Patent
- LA English
- FAN.CNT 3

|      | 0111           |            |           | ·               |          |
|------|----------------|------------|-----------|-----------------|----------|
|      | PATENT NO.     | KIND .     | DATE      | APPLICATION NO. | DATE     |
| ΡI   | US 5624941     | A          | 1997.0429 | US 1994-348881  | 19941129 |
|      | FR 2692575     | A1         | 19931224  | FR 1992-7645    | 19920623 |
|      | FR 2692575     | B1         | 19950630  |                 | • •      |
|      | FR 2713224     | <b>A</b> 1 | 19950609  | FR 1993-14444   | 19931202 |
|      | FR 2713224     | B1         | 19960301  |                 |          |
|      | FR 2713225     | . A1       | 19950609  | FR 1994-8974    | 19940720 |
|      | FR 2713225     | B1         | 19960301  |                 |          |
| •    | ZA 9409342     | Α          | 19951009  | ZA 1994-9342    | 19941124 |
|      | JP 2001026541  | A2         | 20010130  | _JP_2000=238472 | 19941202 |
| PRAI | FR 1992-7645   | Α          | .19920623 | •               |          |
| •    | US 1993-79870  | B2         | 19930623  | •               |          |
|      | FR 1993-14444  | Α          | 19931202  |                 |          |
|      | US 1993-168237 | B2         | 19931217  |                 |          |
|      | FR 1994-8974   | Α          | 19940720  |                 |          |
|      | JP 1994-300016 | <b>A</b> 3 | 19941202  | •               |          |
|      |                |            |           |                 |          |

- OS MARPAT 127:5085
- AB Title compds. I [R, R1 = (un) substituted Ph; R2 = H, alkyl; R3 = amino, (un) substituted alkyl, cycloalkyl aryl, heterocyclic; X = bond, NR4, CH2NR4; R4 = H, alkyl] were prepd. and have cannabinoid receptor affinity (no data). Thus, 4-ClC6H4COEt was treated with EtO2CCO2Et to give 4-ClC6H4C(OLi):CMeCOCO2Et which was cyclized with 2,4-Cl2C6H3NHNH2 to give I [R = 2,4-Cl2C6H3, R1 = 4-ClC6H4, R2 = Me, X = bond, R3 = OEt]. The ester was hydrozyled to the acid, converted to the chloride, and amidated with 1-aminopiperidine to give I [R = 2,4-Cl2C6H3, R1 = 4-ClC6H4, R2 = Me, X = bond, R3 = piperidinoamino].
- IT 158939-48-1P
  - RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
  - (prepn. of diarylpyrazoles as cannabinoid receptor agonists)
- RN 158939-48-1 CAPLUS
- CN 1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-(octahydro-4,7-methano-1H-inden-5-yl)- (9CI) (CA INDEX NAME)

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L4
     ANSWER 8 OF 16 CAPLUS COPYRIGHT 2003 ACS
ÄΝ
     1994:680631 CAPLUS
DN
     121:280631
     Preparation of pyrazole derivatives as cannabinoid receptor ligands
ΤI
IN
     Barth, Francis; Casellas, Pierre; Congy, Christian; Martinez, Serge;
     Carmona, Murielle
     Elf Sanofi, Fr.
PA
SO
     Eur. Pat. Appl., 66 pp.
     CODEN: EPXXDW
DT
     Patent
LA
     French
FAN.CNT 3
     PATENT NO.
                       KIND
                             DATE
                                             APPLICATION NO.
                                                               DATE
PΙ
     EP 576357
                       A1
                             19931229
                                             EP 1993-401614
                                                               19930623
     EP 576357
                       В1
                             19970305
         R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE
     FR 2692575
                             19931224
                       A1
                                             FR 1992-7645
                                                               19920623
     FR 2692575
                       В1
                             19950630
     CZ 289487
                       В6
                             20020213
                                             CZ 1993-1172
                                                               19930616
     BR 9302435
                        Α
                             19940111
                                             BR 1993-2435
                                                               19930621
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                        AΑ
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                                             CA 1993-2098944
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     NO-9302296
                             <del>-1-9:93:1-2:2-7-</del>
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     IL 106099
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                                             IL 1993-106099
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     RU 2119917
                        C1
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                                             RU 1993-49108
                                                               19930622
     TW 494096
                        В
                                             TW 1993-82104910 19930622
                             20020711
     AU 9341438
                       A1
                             19940106
                                             AU 1993-41438
                                                               19930623
                             19951109
     AU 664281
                       B2
     HU 64526
                       Α2
                             19940128
                                             HU 1993-1851
                                                               19930623
     HU 218797
                       В
                             20001228
     ZA 9304511
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                       Α
                             19940222
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                             19940315
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                       B2
                             20011217
     AT 149489
                       \mathbf{E}
                             19970315
                                             AT 1993-401614
                                                               19930623
     ES 2101258
                        Т3
                             19970701
                                             ES 1993-401614
                                                               19930623
PRAI FR 1992-7645
                       Α
                             19920623
     MARPAT 121:280631
AB
     Title compds. [I; R = NR1R2, R2[X = (CH2)xNR3], R5(X = bond); R1,R2 = R1
     alkyl, Ph, heterocyclyl, etc.; NR1R2 = heterocyclyl; R3,R4 = H, alkyl; R5
     = (cyclo)alkyl, phenylalkyl, etc.; R6,R7 = (substituted)Ph; X = bond,
     (CH2) xNR3; x = 0 or 1] were prepd. as cannabinoid receptor ligands (no
     data). Thus, 4-ClC6H4COMe was condensed with CH2(CO2Et)2 in NaOMe/MeOH
     and the product condensed with 2,4-C12C6H3NHNH2 to give I (R4 = H, R6 =
     2,4-Cl2C6H3, R7 = 4-ClC6H4, X = bond)(II; R = OMe) and the corresponding
     acid chloride(2 steps) was condensed with 2-adamantanamine to give II (R =
     2-adamantyl).
IT
     158939-48-1P
     RL: SPN (Synthetic preparation); PREP (Preparation)
        (prepn. of, as cannabinoid receptor ligand)
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1H-Pyrazole-3-carboxamide, 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-N-

(octahydro-4,7-methano-1H-inden-5-yl)- (9CI) (CA INDEX NAME)

RN

158939-48-1 CAPLUS

L4 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2003 ACS

AN 1985:498330 CAPLUS

DN 103:98330

TI Amides of N-phenylbenzonorbornen-2-endo-amine with hypotensive and other activities

AU Longobardi, M.; Schenone, P.; Bargagna, A.; Berrino, L.; Matera, C.; Marmo, E.

CS Ist. Sci. Farm., Univ. Genova, Genoa, Italy

SO Farmaco, Edizione Scientifica (1985), 40(3), 152-61 CODEN: FRPSAX; ISSN: 0430-0920

DT Journal

LA English

AB The title compds. I (R = Me, cyclopropyl, CH:CHPh, (un)substituted Ph, CH2NEt2, pyrrolidinomethyl, etc.) were prepd. and tested for pharmacol. activity. Some I showed a marked hypotensive activity in rats, whereas most I induced a moderate local anesthesia in mice. I affected the heart rate and had a weak antiarrhythmic activity.

IT 96356-24-0P 96356-25-1P 96356-26-2P 96356-27-3P

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP

(Preparation); PROC (Process); USES (Uses) (prepn. and pharmacol. of)

(preph. and pha)

RN 96356-24-0 CAPLUS

CN 1-Pyrrolidineacetamide, N-phenyl-N-(1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-yl)-, (1.alpha.,2.beta.,4.alpha.)- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 96356-25-1 CAPLUS

CN 1-Piperidineacetamide, N-phenyl-N-(1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-yl)-, (1.alpha.,2.beta.,4.alpha.)- (9CI) (CA INDEX NAME)

RN 96356-26-2 CAPLUS

CN 4-Morpholineacetamide, N-phenyl-N-(1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-yl)-, (1.alpha.,2.beta.,4.alpha.)- (9CI) (CA INDEX NAME)

RN 96356-27-3 CAPLUS

CN 1-Piperazineacetamide, 4-methyl-N-phenyl-N-(1,2,3,4-tetrahydro-1,4-methanonaphthalen-2-yl)-, (1.alpha.,2.beta.,4.alpha.)- (9CI) (CA INDEX NAME)

L4 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2003 ACS

AN 1985:197548 CAPLUS

DN 102:197548

TI Synthesis and pharmacological activity of derivatives of exo-trimethylenenorbornane. V

AU Longobardi, M.; Schenone, P.; Bargagna, A.; Matera, C.; Rossi, F.; Marmo, E.

CS Ist. Sci. Farm., Univ. Genova, Genoa, Italy

SO Farmaco, Edizione Scientifica (1985), 40(3), 162-9 CODEN: FRPSAX; ISSN: 0430-0920

DT Journal

LA English

ΙT

AB Seven amides I (R = CH2Cl, Me, cyclopropyl, CH:CHPh, Ph, 4-NO2C6H4, and 4-H2NC6H4) and 6 glycinamides II (R = NEt2, NMe(CH2)2NMe2, pyrrolidino, piperidino, morpholino, N'-methylpiperazino) derived from N-phenyl-exo-5,6-trimethylenenorbornan-2-endo-amine [96356-45-5] were prepd. and tested for pharmacol. activity. All of the I derivs. showed moderate hypotensive activity whereas some of the I and II derivs. had weak local anesthetic and antiarrhythmic activity. The effects of the compds. on heart rate are also described.

96356-40-0P 96356-41-1P 96356-42-2P

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic

preparation); THU (Therapeutic/use); BIOL (Biological study); PREP
(Preparation); PROC (Process); USES (Uses)

(prepn. and pharmacol. of)

RN 96356-40-0 CAPLUS

CN 1-Pyrrolidineacetamide, N-(octahydro-4,7-methano-1H-inden-5-yl)-N-phenyl-, (3a.alpha.,4.beta.,5.alpha.,7.beta.,7a.alpha.)- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 96356-41-1 CAPLUS

CN 1-Piperidineacetamide, N-(octahydro-4,7-methano-1H-inden-5-yl)-N-phenyl-, (3a.alpha.,4.beta.,5.alpha.,7.beta.,7a.alpha.)- (9CI) (CA INDEX NAME)

RN 96356-42-2 CAPLUS

CN 4-Morpholineacetamide, N-(octahydro-4,7-methano-1H-inden-5-yl)-N-phenyl-, (3a.alpha.,4.beta.,5.alpha.,7.beta.,7a.alpha.)- (9CI) (CA INDEX NAME)

Relative stereochemistry.

RN 96356-43-3 CAPLUS

CN 1-Piperazineacetamide, 4-methyl-N-(octahydro-4,7-methano-1H-inden-5-yl)-N-phenyl-, (3a.alpha.,4.beta.,5.alpha.,7.beta.,7a.alpha.)- (9CI) (CA INDEX NAME)

L4ANSWER 11 OF 16 CAPLUS COPYRIGHT 2003 ACS

AN 1983:34595 CAPLUS

DN 98:34595

ΤI 5-Fluorouracil derivatives, and their pharmaceutical compositions

IN Takaya, Takao; Tozuka, Zenzaburo

PA Fujisawa Pharmaceutical Co., Ltd., USA

U.S., 20 pp. Cont.-in-part of U.S. Ser. No. 89,399, abandoned. SO

CODEN: USXXAM

DT Patent

English LA

| FAN. | CNT 2          |    |                        |                 |          |  |
|------|----------------|----|------------------------|-----------------|----------|--|
|      | PATENT NO.     |    | DATE                   | APPLICATION NO. | DATE     |  |
|      |                |    |                        |                 |          |  |
| PI   | US 4349552     | Α  | 19820914               | US 1980-111643  | 19800114 |  |
|      | JP 55081865    | A2 | 19800620               | JP 1979-140983  | 19791030 |  |
|      | ES 485554      | A1 | 19801101               | ES 1979-485554  | 19791030 |  |
| PRAI | GB 1978-42426  | •  | 19781030               |                 |          |  |
|      | GB 1979-2195   |    | 19790122               |                 |          |  |
|      | GB 1979-9522   |    | 19790319               |                 |          |  |
|      | GB 1979-19439  |    | 19790604               |                 |          |  |
|      | CA 1979-338650 |    | 19791029               |                 |          |  |
|      | JP 1979-140983 |    | 19791030               |                 |          |  |
|      | US-1979=89399  |    | <del>-1979103</del> 0- |                 |          |  |

AΒ Carbamoyluracils I [R = (un)substituted norbornyl, bicyclo[2.2.2]octyl, bicyclo[3.1.1]heptyl, adamantyl] were prepd. Thus 1-adamantylacetic acid was treated with N3P(O)(OPh)2 to give 1-adamantylmethyl isocyanate which was treated with 5-fluorouracil to give I (R = 1-adamantylmethyl) (II). At 100 mg/kg day for 4 days orally to leukemia P388-infected mice, II gave a 50% increase in life span vs. controls.

IT 76198-22-6P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(prepn. and antitumor activity of)

RN 76198-22-6 CAPLUS

CN 4,7-Methano-1,3-benzodioxole-5-carboxylic acid, 6-[[(5-fluoro-3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl)carbonyl]amino]hexahydro-2,2-dimethyl-, ethyl ester (9CI) (CA INDEX NAME)

L4 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2003 ACS

AN 1981:47313 CAPLUS

DN 94:47313

TI 5-Fluorouracil derivatives and their pharmaceutical compositions

IN Takaya, Takao; Tozuka, Zenzaburo

PA Fujisawa Pharmaceutical Co., Ltd., Japan

SO Eur. Pat. Appl., 87 pp.

CODEN: EPXXDW

DT Patent

LA English

FAN.CNT 2

| LTM. | ~14 T      | 2    |       |      |        |        |      |         |        |        |       | _       |    |
|------|------------|------|-------|------|--------|--------|------|---------|--------|--------|-------|---------|----|
|      | PATENT NO. |      | KIND  | DATE |        |        | AP   | PLICATI | ON NO. | DATE   |       |         |    |
|      |            |      |       |      |        |        | ·    |         |        |        |       |         |    |
| ΡÏ   | ΕP         | 1094 | 1     |      | A1     | 19800  | 514  |         | EP     | 1979-3 | 02358 | 1979102 | 29 |
|      | ΕP         | 1094 | 1     |      | B1     | 19820  | 512  |         |        |        |       |         |    |
|      |            | R:   | AT,   | BE,  | CH, DE | E, FR, | GB,  | IT,     | LU, I  | NL, SE |       |         |    |
|      | ΑT         | 1011 |       |      | E      | 19820  | 515  |         | AΤ     | 1979-3 | 02358 | 1979102 | 29 |
|      | ES         | 4855 | 54    |      | A1     | 19801  | 101  |         | ES     | 1979-4 | 85554 | 1979103 | 30 |
| PRAI | GB         | 1978 | -4242 | 26   |        | 19781  | .030 |         |        |        |       | •       |    |
|      | GB         | 1979 | -2195 | 5    |        | 19790  | 122  |         |        |        | 1     | `       |    |
|      | GB         | 1979 | -9522 | 2    |        | 19790  | 319  |         |        |        | X     | )       |    |
|      | GB         | 1979 | -1943 | 39   |        | 19790  | 604  |         |        |        |       | /       |    |
|      | EΡ         | 1979 | -3023 | 358  |        | 19791  | 029  |         |        |        | /     |         |    |
|      |            |      |       |      |        |        |      |         |        |        |       |         |    |

AB Fluorouracils I [R = (un) substituted bridged alicyclic, alkyl, alkenyl, aryl, heterocyclyl, carboxylic acid, and ester] were prepd. Thus, treating 3.88 g II (R1 = CO2H) with 5.50 g (PhO) 2P(O) N3 gave II (R1 = NCO), which was treated with 2.60 g 5-fluorouracil to give 1.85 g I (R = 1-adamantylmethyl). The latter compd. increased the survival time of leukemia P-388-infected mice by 50% over controls when given at 100 mg/kg day orally for 4 days.

IT 76198-22-6P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(prepn. and antitumor activity of)

RN 76198-22-6 CAPLUS

CN 4,7-Methano-1,3-benzodioxole-5-carboxylic acid, 6-[[(5-fluoro-3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinyl)carbonyl]amino]hexahydro-2,2-dimethyl-, ethyl ester (9CI) (CA INDEX NAME)

L4 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2003 ACS

AN 1980:141624 CAPLUS

DN 92:141624

TI A molecular receptor model for carboxin

AU Schewe, T.; Mueller, W.; Lyr, H.; Zanke, D.

CS Inst. Physiol. Biol. Chem., Humboldt-Univ. Berlin, Berlin, Ger. Dem. Rep.

SO Abhandlungen der Akademie der Wissenschaften der DDR, Abteilung Mathematik, Naturwissenschaften, Technik (1979), (2N, Vortr. Int. Sym p.: Systemfungiz., 5th, 1977), 241-51 CODEN: AAWTD2; ISSN: 0138-1059

DT Journal

LA German

AB Data are given on the in vitro effect of 24 carboxin [5234-68-4] derivs. and analogs I (R = H, tert-Bu, cyclopentyl, cyclohexyl, Ph, substituted Ph, .alpha.-naphthyl, etc) and R'CONHPh (R' = 2-methyl-1,4-oxanthiin-3-yl, o-tolyl, o-hydroxyphenyl, 2-methyl-1,4-oxanthiin-3-yl dioxide, etc) on succinate cytochrome c reductase [9028-10-8] from cattle heart mitochondrial nonphosphorylating electron-transport particles (Mueller, W., et al., 1977). The succinate dehydrogenase subunit high-potential Fe-S protein (Fe S-center S3) seems to be the specific receptor, and the interaction seems to involve the hydrophobic group at the amide-N, the 2-cis-Me of the oxathiin cycle, and the vinylogous CO group. A model is given, by which the electrophilic C of the .alpha.-.beta.-unsatd. GO-group-is bound to the cysteine-S of the Fe-S cluster, whereas the N and O are bound coordinatively to 2 different Fe atoms of the cluster.

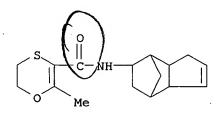
IT 65132-71-0

RL: PROC (Process)

(binding of, to succinate dehydrogenase high-potential iron-sulfur protein, mol. receptor model in relation to)

RN 65132-71-0 CAPLUS

CN 1,4-Oxathiin-3-carboxamide, N-(3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-6-yl)-5,6-dihydro-2-methyl- (9CI) (CA INDEX NAME)





L4 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2003 ACS

AN 1978:32999 CAPLUS

DN 88:32999

TI Effective mechanisms of respiratory inhibition by the fungicides of the carboxin group. Effect of oxathiin derivatives and analogs on nonphosphorylating submitochondrial particles from beef heart

AU Mueller, W.; Schewe, T.; Lyr, H.; Zanke, D.

CS Inst. Physiol. Biol. Chem., Humboldt-Univ., Berlin, Ger. Dem. Rep.

SO Zeitschrift fuer Allgemeine Mikrobiologie (1977), 17(5), 359-72 CODEN: ZAPOAK; ISSN: 0044-2208

DT Journal

LA German

The inhibitory activity of carboxin (I, R = Ph) [5234-68-4] and of 22 AB derivs. and analogs, such as I (R = H, cycloalkyl, .alpha.-naphthyl, substituted Ph, etc.) was tested on the succinate-cytochrome c reductase [9028-10-8] and NADH oxidase [9032-21-7] of nonphosphorylating electron-transport particles (ETP) from cattle-heart mitochondria. Some I were also tested on particulate succinic dehydrogenase [9002-02-2] of the carboxin-sensitive Trametes versicolor and carboxin-resistant Trichoderma viride. The inhibitory activity of I on ETP cytochrome c oxidoreductase correlated well with that on succinic dehydrogenase of Trametes versicolor, but not with that on succinic dehydrogenase of Trichoderma viride. Thus, cattle-heart ETP is a suitable model for carboxinreceptors. Low correlation was shown between the activity of I on cytochrome c oxidoreductase and the hydrophobicity parameter lg P of I (P is the octanol to water distribution coeff.). Electronic and steric effects were also evident. A multicenter mechanism is suggested for the receptor-binding of I. Mechanism of resistance to I is discussed.

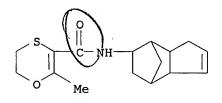
IT 65132-71-0

RL: BIOL (Biological study)

(respirationry enzymes inhibition by, in cattle heart mitochondrial particles, receptors in fungi in relation to)

RN 65132-71-0 CAPLUS

CN 1,4-Oxathiin-3-carboxamide, N-(3a,4,5,6,7,7a-hexahydro-4,7-methano-1H-inden-6-yl)-5,6-dihydro-2-methyl- (9CI) (CA INDEX NAME)





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L4 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2003 ACS
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AN 1972:46068 CAPLUS

DN 76:46068

TI Fungicidal N-cycloalkyl-2,5-dimethylfuran-3-carboxamides

IN Distler, Harry; Widder, Rudi; Pommer, Ernst H.

PA Badische Anilin- und Soda-Fabrik A.-G.

SO Ger. Offen., 11 pp.

CODEN: GWXXBX

DT Patent

LA German

FAN.CNT 1

| FAN. | CNT        | 1 .          |            |          |     |                           |                        |
|------|------------|--------------|------------|----------|-----|---------------------------|------------------------|
|      | PAT        | ENT NO.      | KIND       | DATE     | AP  | PLICATION NO.             | DATE                   |
| PI   |            | 2019535      | A          | 19711104 | DE  | 1970-2019535              | 19700423               |
|      |            | 2019535      | B2         | 19730405 |     |                           | ·                      |
|      | DE         | 2019535      | C3         | 19870212 |     | •                         |                        |
|      | US         | 3862966      | Α          | 19750128 | US  | 1971-131545               | 19710405               |
|      | ZΑ         | 7102428      | Α          | 19720223 | ZA  | 1971-2428                 | 19710415               |
|      | NL         | 7105249      | Α          | 19711026 | NL  | 1971-5249                 | 19710419               |
|      | CA         | 939364       | A1         | 19740101 | CA  | 1971-110754               | 19710419               |
|      | SE         | 394675       | · В        | 19770704 | SE  | 1971-5109                 | 19710420               |
|      | HU         | 162532       | P          | 19730328 | HU  | 1971-BA2571               | 19710421               |
|      | BE         | 766110       | A1         | 19711022 | BE- | -197 <del>1-1</del> 02516 | <del>-19710422</del> - |
|      | AΤ         | 305694       | ·B         | 19730312 | AT  | 1971-3467                 | 19710422               |
|      | GB         | 1338834      | Α          | 19731128 | GB  | 1971-10767                | 19710422               |
|      | DK         | 128221       | В          | 19740325 | DK  | 1971-1937                 | 19710422               |
|      | ·SU        | 434635       | D          | 19740630 | SU  | 1971-1651491              | 19710422               |
|      | $_{ m PL}$ | 77193        | P          | 19750430 | PL  | 1971-147718               | 19710422               |
|      | CS         | 165976       | P          | 19751222 | CS  | 1971-2925                 | 19710422               |
|      | FR         | 2090665      | <b>A</b> 5 | 19720114 | FR  | 1971-14632                | 19710423               |
|      | CH         | 539388       | Α          | 19730914 | CH  | 1971-5950                 | 19710423               |
|      | US         | 3903293      | Α          | 19750902 | US  | 1973-361811               | 19730518               |
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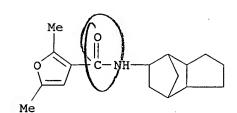
AB Title compds. (I; R=H or Me, R1=tricyclodecyl, cyclohexyl, or methylcyclohexyl), useful as, e.g. sprays and powders, were prepd. in 86.5-98.9% yield by reaction of 2,5-dimethylfuran-3-carbonyl chloride (II) with HNRR1 and used at 0.005-0.01% against, e.g. Rhizoctonia solani and Uromyces appendiculatus. Thus, II and Et3N were simultaneously added to cyclohexylamine in ClCH2CH2Cl at 25-35.degree. and the mixt. was stirred 3 hr at 35.degree. to give 96.8% I (R=H, R1=cyclohexyl). Similarly prepd. were 5 other I, e.g. (R and R1 given): Me, cyclohexyl; and H, tricyclo[5.2.1.02,6]dec-8-yl. Compns. contg. I were reported.

IT 34849-41-7P

RL: SPN (Synthetic preparation); PREP (Preparation)
 (prepn. of)

RN 34849-41-7 CAPLUS

CN 3-Furancarboxamide, 2,5-dimethyl-N-(octahydro-4,7-methano-1H-inden-5-yl)-(9CI) (CA INDEX NAME)





L4 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2003 ACS

AN 1965:2797 CAPLUS

DN 62:2797

OREF 62:460e-g

TI N-(5,6-Dihydrodicyclopentadien-5-yl)ureas as herbicides

PA Farbwerke Hoechst A.-G.

SO 15 pp.

DT Patent

LA Unavailable

FAN.CNT 1

19621011

PRAI DE

AB 5,6-Dihydrodicyclopentadien-5-yl isocyanate (I) is treated with amines to give compds. of the general formula II. COCl2 is introduced into a mixt. of 223 g. 5,6-dihydrodicyclopentadien-5-ylamine in 250 ml. PhMe at between -5.degree. and 0.degree. and the mixt. agitated 1/2 hr. and heated to 100-10.degree. to give 95.5% I, b8 111-13.degree., n20D 1.5188. I (0.3 mole) is dissolved in 200 ml. PhMe, 38 g. 40% Me2NH added in 20 min., the temp. rises to 40.degree., and the mixt. agitated 3 hrs. at 40.degree., cooled, and filtered to give 64 g. N-(5,6-dihydrodicyclopentadien-5-yl)-N1,N1-dimethylurea (III), m. 151-2.degree. (petr. ether). Similarly prepd. are the following II (R, R1, and m.p. given): Me, MeO, 78-9.degree.

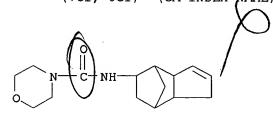
prepd. are the following II (R, Rl, and m.p. given): Me, MeO, 78-9.degree (petr. ether); iso-Bu, iso-Bu, 136-7.degree. (PhMe). A compn. contg. 25% III, 64% active H4SiO4, 10% cellulose pitch, and 1% Na salt of oleic acid methyltauride is prepd.

IT 4313-64-8, 4-Morpholinecarboxamide, N-(3a,4,5,6,7,7a-hexahydro-4,7-methanoinden-5-yl)-

(prepn. of)

RN 4313-64-8 CAPLUS

CN 4-Morpholinecarboxamide, N-(3a,4,5,6,7,7a-hexahydro-4,7-methanoinden-5-yl)-(7CI, 8CI) (CA INDEX NAME)



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L5 ANSWER 1 OF 1 CAOLD COPYRIGHT 2003 ACS

AN CA62:460e CAOLD

TI N-(5,6-dihydrodicyclopentadien-5-yl)ureas as herbicides

PA Farbwerke Hoechst A.-G.

DT Patent

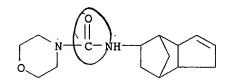
PATENT NO. KIND DATE

PI FR 1372831

IT 4313-64-8

RN 4313-64-8 CAOLD

CN 4-Morpholinecarboxamide, N-(3a,4,5,6,7,7a-hexahydro-4,7-methanoinden-5-yl)-(7CI, 8CI) (CA INDEX NAME)



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| FULL ESTIMATED COST                        | ENTRY<br>3.02       | SESSION<br>224.77 |
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# Sleep apnea

**Date** 2003/6/30 18:00:01 **Topic:** Sleep

Sleep apnea is a serious, potentially lifethreatening condition that is far more common than generally understood. First described in 1965, sleep apnea is a breathing disorder characterized by brief interruptions of breathing during sleep. It owes its name to a Greek word, apnea, meaning "want of breath." There are two types of sleep apnea: central and obstructive. Central sleep apnea, which is less common, occurs when the brain fails to send the appropriate signals to the breathing muscles to initiate respirations.

Obstructive-sleep-apnea-is-far-more-common and occurs when air cannot flow into or out of the person's nose or mouth although efforts to breathe continue.

In a given night, the number of involuntary breathing pauses or "apneic events" may be as high as 20 to 30 or more per hour. These breathing causes are almost always accompanied by snoring between apnea episodes, although not everyone who snores has this condition. Sleep apnea can also be characterized by choking sensations. The frequent interruptions of deep, restorative sleep often lead to early morning headaches and excessive daytime sleepiness. Early recognition and treatment of sleep apnea is important because it may be associated with irregular heartbeat, high blood pressure, heart attack, and stroke.

#### WHO GETS SLEEP APNEA?

Sleep apnea occurs in all age groups and both sexes but is more common in men (it may be underdiagnosed in women) and possibly young African Americans. It has been estimated that as many as 18 million Americans have sleep apnea. Four percent of middle-aged men and 2 percent of middle-aged women have sleep apnea along with excessive daytime sleepiness. People most likely to have or develop sleep apnea include those who snore loudly and also are overweight, or have high blood pressure, or have some physical abnormality in the nose, throat, or other parts of the upper airway.

Sleep apnea seems to run in some families, suggesting a possible genetic basis.

## WHAT CAUSES SLEEP APNEA?

Certain mechanical and structural problems in the airway cause the interruptions in breathing during sleep. In some people, apnea occurs when the throat muscles and tongue relax during sleep and partially block the opening of the airway. When the muscles of the soft palate at the base of the tongue and the uvula (the small fleshy tissue hanging from the center of the back of the throat) relax and sag, the airway becomes blocked, making breathing labored and noisy and even stopping it altogether. Sleep apnea also can occur in obese people when an excess amount of tissue in the airway causes it to be narrowed. With a narrowed airway, the person continues his or her efforts to breathe, but air cannot easily flow into or out of the nose or mouth. Unknown to the person, this results in heavy snoring, periods of no breathing,

and frequent arousals (causing abrupt changes from deep sleep to light sleep).

Ingestion of alcohol and sleeping pills increases the frequency and duration of breathing pauses in people with sleep apnea.

## HOW IS NORMAL BREATHING RESTORED DURING SLEEP?

During the apneic event, the person is unable to breathe in oxygen and to exhale carbon dioxide, resulting in low levels of oxygen and increased levels of carbon dioxide in the blood. The reduction in oxygen and increase in carbon dioxide alert the brain to resume breathing and cause an arousal. With each arousal, a signal is sent from the brain to the upper airway muscles to open the airway;

breathing is resumed, often with a loud snort or gasp. Frequent arousals, although necessary for

breathing to restart, prevent the patient from getting enough restorative, deep sleep.

## WHAT ARE THE EFFECTS OF SLEEP APNEA?

Because of the serious disturbances in their normal sleep patterns, people with sleep apnea often-feel-very sleepy during the day and their concentration

and daytime performance suffer. The lifethreatening. They include depression, irritability, sexual dysfunction, learning and memory difficulties, and falling asleep while at work, on the phone, or driving. It has been estimated that up to 50 percent of sleep apnea patients have high blood pressure. Although it is not known with certainty if there is a cause and effect relationship, it appears that sleep apnea contributes to high

blood pressure. Risk for heart attack and stroke may also increase in those with sleep apnea. In addition, sleep apnea is sometimes implicated in sudden infant death syndrome.

## WHEN SHOULD SLEEP APNEA BE SUSPECTED?

For many sleep apnea patients, their spouses are the first ones to suspect that something is wrong, usually from their heavy snoring and apparent struggle to breathe. Coworkers or friends of the sleep apnea victim may notice that the individual falls asleep during the day at inappropriate times (such as while driving a car, working, or talking). The patient often does not know he or she has a problem and may not believe it when told. It is important that the person see a doctor for evaluation of the sleep problem.

# HOW IS SLEEP APNEA DIAGNOSED?

In addition to the primary care physician, pulmonologists, neurologists, or other physicians with specialty training in sleep disorders may be involved in making a definitive diagnosis and initiating treatment. Diagnosis of sleep apnea is not simple because there can be many different

reasons for disturbed sleep.

## Several tests are available for evaluating

a person for sleep apnea. Polysomnography is a test that records a variety of body functions during sleep, such as the electrical activity of the brain, eye movement, muscle activity, heart rate, respiratory effort, air flow, and blood

oxygen levels. These tests are used both to diagnose sleep apnea and to determine its severity.

The Multiple Sleep Latency Test (MSLT) measures the speed of falling asleep. In this test, patients are

given several opportunities to fall asleep during the course of a day when they would normally be awake.

For each opportunity, time to fall asleep is measured. People without sleep problems usually take an average of 10 to 20 minutes to fall

asleep. Individuals who fall asleep in less than 5 minutes are likely to require some treatment for sleep disorders.

The MSLT may be useful to measure the degree of excessive daytime sleepiness and to rule out other

types of sleep disorders. Diagnostic tests usually are performed in a sleep center, but new technology

may allow some sleep studies to be conducted in the patient's home.

# HOW IS SLEEP APNEA TREATED?

The specific therapy for sleep apnea is tailored to the individual patient based on medical history, physical examination, and the results of polysomnography. Medications are generally not effective in the treatment of sleep apnea. Oxygen administration may safely benefit certain patients but does not eliminate sleep apnea or prevent daytime sleepiness. Thus, the role of oxygen in the treatment of sleep apnea is controversial, and it is difficult to predict which patients will respond well. It is important that the effectiveness of the selected treatment be verified; this is usually accomplished by polysomnography.

## Behavioral Therapy

Behavioral changes are an important part of the treatment program, and in mild cases behavioral therapy may be all that is needed. The individual should avoid the use of alcohol, tobacco, and sleeping pills, which make the airway more likely to collapse during sleep and prolong the apneic periods. Overweight persons can benefit from losing weight. Even a 10 percent weight loss can reduce the number of apneic events for most patients. In some patients with mild sleep apnea, breathing pauses occur only when they sleep on their backs.

In such cases, using pillows and other devices that help them sleep in a side position is often helpful.

# Physical or Mechanical Therapy

Nasal continuous positive airway pressure (CPAP) is the most common effective treatment for sleep apnea. In this procedure, the patient wears a mask over the nose during sleep, and pressure from an air blower forces air through the nasal passages. The air pressure is adjusted so that it is just enough to prevent the throat from collapsing during sleep. The pressure is constant and continuous.

Nasal CPAP prevents airway closure while in use, but apnea episodes return when CPAP is stopped or

used improperly. Variations of the CPAP device

attempt to minimize side effects that sometimes occur, such as nasal irritation and drying, facial skin irritation, abdominal bloating, mask leaks, sore eyes, and headaches. Some versions of CPAP vary the pressure to coincide with the person's breathing pattern, and others start with low pressure, slowly

increasing it to allow the person to fall asleep before the full prescribed pressure is applied.

Dental appliances that reposition the lower jaw and the tongue have been helpful to some

patients with

mild sleep apnea or who snore but do not have apnea. Possible side effects include damage to teeth, soft tissues, and the jaw joint. A dentist

or orthodontist is often the one to fit the patient with such a device. Surgery Some patients with sleep apnea may need surgery. Although several surgical procedures are used to increase the size of the airway, none of them is completely successful or without risks. More than one procedure may need to be tried before the patient realizes any benefits.

Some of the more common procedures include removal of adenoids and tonsils (especially in children), nasal polyps or other growths, or other tissue in the airway and correction of structural deformities. Younger patients seem to benefit from these surgical procedures more than older patients.

Uvulopalatopharyngoplasty (UPPP) is a procedure used to remove excess tissue at the back of the throat (tonsils, uvula, and part of the soft palate).

The success of this technique may range from 30 to 50 percent. The long-term side effects and benefits are not known, and it is difficult to predict which patients will do well with this procedure.

Laser-assisted uvulopalatoplasty (LAUP) is done to eliminate snoring but has not been shown to be effective in treating sleep apnea. This procedure

involves-using-a-laser-device-to-eliminate tissue in the back of the throat. Like UPPP, LAUP may

decrease or eliminate snoring but not sleep apnea itself. Elimination of snoring, the primary symptom of sleep apnea, without influencing the condition

may carry the risk of delaying the diagnosis and possible treatment of sleep apnea in patients who elect LAUP. To identify possible underlying

sleep apnea, sleep studies are usually required before LAUP is performed. Tracheostomy is used in persons with severe, life-threatening sleep apnea. In this procedure, a small hole is made inthe windpipe and a tube is inserted into the opening. This tube stays closed during waking hours, and the

person breathes and speaks normally. It is opened for sleep so that air flows directly into the lungs, bypassing any upper airway obstruction. Although

this procedure is highly effective, it is an extreme measure that is poorly tolerated by patients and rarely used. Other procedures. Patients in whom

sleep apnea is due to deformities of the lower jaw may benefit from surgical reconstruction. Finally, surgical procedures to treat obesity are sometimes

recommended for sleep apnea patients who are morbidly obese.

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S3226, a novel NHE3 inhibitor, attenuates ischemia-induced acute renal failure in rats.

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BACKGROUND: Acute renal failure (ARF) remains a major problem in clinical nephrology characterized by sudden loss of the kidney function due to ischemia, trauma, and/or nephrotoxic drugs. The current therapy of ARF is symptomatic with mortality rates exceeding 50%. The aim of this study was to investigate the effects of an intravenous infusion of S3226 (3-[2-(3-guanidino-2-methyl-3-oxopropenyl)-5-methyl-phenyl]-Nisopropylidene-2-methyl-acrylamide dihydrochloride), a selective Na+/H+ exchange subtype 3 (NHE3) blocker, in ischemia-induced ARF in rats. In a second series of experiments cytosolic pH (pHi) changes in the kidney during ARF were continuously measured by means of nuclear magnetic resonance spectroscopy (MRS). METHODS: ARF was induced by bilateral occlusion of renal arteries for 40 minutes in three groups of anaesthetized Wistar rats. Control rats (N = 12) were infused with saline (6.25 mL/kg over 30 min) before occlusion and the compound groups (each N = 12) were infused with S3226 at a dose of 20 mg/kg over 30 minutes either before initiation of ischemia or immediately after release of clamps. Plasma creatinine (PCr), creatinine clearance (CCr), urine volume, sodium, and potassium excretion were determined up to seven days after release of clamps. In the second series of experiments in anaesthetized rats the left kidney was exposed by flank incision and fixed in a non-magnetic device. An inflatable cuff was positioned around the pedicle to induce ischemia without removing animals from the magnet. A double-tuned 1H-31P home-built surface coil was placed above the exposed kidney for the detection of pHi. RESULTS: At day 1 after ischemia CCr in the control group was significantly lower as compared to S3226-treated animals (control 0.30 +/- 0.05 vs. before 0.90 +/- 0.26 and reperfusion 0.83 +/- 0.15 mL/min/kg, respectively). PCr increased from 18 +/- 0.1 micromol/L before occlusion to 245 +/- 7 micromol/L in the control. The increase in PCr was significantly lower in the S3226 treated groups on days 1, 2, and 3 post-infusion. Fractional sodium excretion decreased significantly from 8.17% in the control to 1.42% and 1.88% in the treated groups. Renal pHi was significantly decreased by 0.15 units versus control during reperfusion. Histological examination of the kidneys on day 7 revealed pronounced reduction of tubular necrosis, dilatation, protein casts and cellular infiltration. CONCLUSIONS: These results demonstrate that an intravenous administration of S3226 acutely improves GFR and kidney function and structure in both treated groups. In addition, in a separate set of studies S3226 significantly decreased post-occlusion renal pHi values. Thus, the inhibition of NHE3 with S3226 may be beneficial in treatment of ischemic ARF.